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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Julia Y. Ljubimova, et al.
Serial No. 09/741,550
Filed: December 19, 2000
For: **USING OVEREXPRESSION OF LAMININ ALPHA 4 SUBUNIT AS A DIAGNOSTIC AND PROGNOSTIC INDICATOR OF MALIGNANT TUMORS**
Examiner: Goldberg, J.A.
Unit: 1634

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RESPONSE TO OFFICE ACTION

Assistant Commissioner for Patents
Washington, D. C. 20231

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BY _____ ANN WEISS
JULY 15, 2002 (DATE OF SIGNATURE)

Dear Sir/Madam:

This is in response to the Office Action mailed June 17, 2002, for the above-captioned patent application. This response is submitted on or before July 17, 2002. In connection with the above-captioned application, the Examiner is respectfully requested to consider the following amendment and remarks concerning election of claim group.

AMENDMENT

A Version With Markings To Show Changes Made is found after Applicant's Remarks.

In the Claims

Please cancel Claims ~~11~~, 12, ~~19~~, 20, ~~30~~, ~~31~~, ~~37-43~~, ~~46~~, ~~47~~, and ~~69-74~~, without prejudice. Please amend Claims 1, 13-16, 18, 21-24, 28, 32-34, 36, 44, 48-50, and 52, and add new Claims 75-78 as follows.

A1

1.(Amended) A method of detecting a malignant tumor in a human subject, comprising:

(a) collecting a sample of a bodily substance containing human nucleic acid, said nucleic acid having originated from cells of the human subject;

(b) detecting quantitatively or semi-quantitatively in the sample a level of expression for *laminin* α4-specific mRNA; and

(c) comparing the expression level in (b) to a level of expression in a normal control, wherein overexpression of *laminin* α4-specific mRNA, with respect to the control, indicates the presence of a malignant tumor in the human subject.

2.(Reiterated) The method of Claim 1, wherein the substance is blood, urine, lymph, cerebrospinal fluid, skin, stroma, vascular epithelium, oral epithelium, vaginal epithelium, cervical epithelium, uterine epithelium, intestinal epithelium, bronchial epithelium, esophageal epithelium, or mesothelium.

3.(Reiterated) The method of Claim 1, wherein the substance is a tissue sample.

4.(Reiterated) The method of Claim 3, wherein the tissue sample is collected from the brain of the subject.

5.(Reiterated) The method of Claim 3, wherein the tissue sample is a tumor tissue.

6.(Reiterated) The method of Claim 1, wherein the bodily substance is plasma.

7.(Reiterated) The method of Claim 1, wherein the bodily substance is a cellular material.

8.(Reiterated) The method of Claim 7, wherein the cellular material is derived from the human subject's brain kidney, bladder, ureter, urethra, thyroid, parotid gland, submaxillary gland, sublingual gland, lymph node, bone, cartilage, lung, mediastinum, breast, uterus, ovary, testis, prostate, cervix uteri, endometrium, pancreas, liver, spleen, adrenal, esophagus, stomach, or intestine.

9.(Reiterated) The method of Claim 1, wherein the neoplastic growth is a carcinoma, sarcoma, lymphoma, mesothelioma, melanoma, glioma, nephroblastoma, glioblastoma, oligodendroglioma, astrocytoma, ependymoma, primitive neuroectodermal tumor, atypical meningioma, malignant meningioma, or neuroblastoma.

10.(Reiterated) The method of Claim 1, wherein the hyperplastic and/or cytologically dysplastic cellular growth or proliferation is benign prostatic hyperplasia/dysplasia or cervical hyperplasia/dysplasia.

A2

13.(Amended) The method of Claim 1, wherein the expression level of *laminin* α4-specific mRNA is detected by measuring RNA.

14.(Amended) The method of Claim 1, wherein the expression level of *laminin* α4-specific mRNA is detected by measuring cDNA.

15.(Amended) The method of Claim 1, wherein a gene expression microarray is used to detect the level of expression of *laminin* α4-specific mRNA.

16.(Amended) The method of Claim 1, further comprising detecting the overexpression of *laminin* β1-specific mRNA relative to the normal control.

17.(Reiterated) The method of Claim 1, further comprising detecting quantitatively or semi-quantitatively in the sample a level of expression with respect to a normal control, of a gene encoding a protein selected from the group consisting of insulin-like growth factor binding protein precursor 3, transforming growth factor-β-induced gene, vascular endothelial growth factor, connective tissue growth factor, human insulin-like growth factor binding protein precursor 5, placental growth factor, transcription factor Ap-2, human insulin-like growth factor II, epidermal growth factor receptor, matrix metalloproteinase-2, keratin 18, vimentin, fibronectin 1, phospholipase A2 receptor, desmoplakin, tropomodulin, tenascin C, and collagen type IV α1 chain, or detecting a combination of expression levels for any of these.

A3

18.(Amended) A method of diagnosing the presence of a glioma in a human subject, comprising:

(a) obtaining a sample from the brain of the human subject;

(b) detecting quantitatively or semi-quantitatively in the sample a level of expression for *laminin* α4-specific mRNA; and

(c) comparing the expression level in (b) to a level of expression in a normal control, wherein overexpression of *laminin* α4-specific mRNA, with respect to the control, indicates the presence of glioma in the subject.

A4

21.(Amended) The method of Claim 18, wherein the expression level of *laminin* α4-specific mRNA is detected by measuring RNA.

22.(Amended) The method of Claim 18, wherein the expression level of *laminin* α4-specific mRNA is detected by measuring cDNA.

23.(Amended) The method of Claim 18, wherein a gene expression microarray is used to detect the level of expression of *laminin* α4-specific mRNA.

A4 concld

24.(Amended) The method of Claim 18, further comprising detecting the overexpression of *laminin* β1-specific mRNA relative to the normal control.

25.(Reiterated) The method of Claim 18, further comprising detecting quantitatively or semi-quantitatively in the sample a level of expression with respect to a normal control, of a gene encoding a protein selected from the group consisting of insulin-like growth factor binding protein precursor 3, transforming growth factor-β-induced gene, vascular endothelial growth factor, connective tissue growth factor, human insulin-like growth factor binding protein precursor 5, placental growth factor, transcription factor Ap-2, human insulin-like growth factor II, epidermal growth factor receptor, matrix metalloproteinase-2, keratin 18, vimentin, fibronectin 1, phospholipase A2 receptor, desmoplakin, tropomodulin, tenascin C, and collagen type IV α1 chain, or detecting a combination of expression levels for any of these.

26.(Reiterated) The method of Claim 18, wherein the sample is a tumor tissue.

27.(Reiterated) The method of Claim 18, wherein the sample comprises plasma.

A5

28.(Amended) A method of predicting the recurrence of a malignant tumor in a human subject from whom a tumor has been resected, comprising:

(a) obtaining a tissue sample from the human subject, said tissue sample being from a region adjacent to the site of the tumor;

(b) detecting quantitatively or semi-quantitatively a level of expression for *laminin* α4-specific mRNA in the sample; and

(c) comparing the expression level in (b) to a level of expression in a normal tissue control, wherein overexpression of *laminin* α4-specific mRNA, with respect to the control, is predictive of a recurrence of a malignant tumor in the subject.

29.(Reiterated) The method of Claim 28, wherein the tissue sample is histopathologically normal in appearance.

A6

32.(Amended) The method of Claim 28, wherein the expression level of *laminin* α4-specific mRNA is detected by measuring RNA.

33.(Amended) The method of Claim 28, wherein the expression level of *laminin* α4-specific mRNA is detected by measuring cDNA.

34.(Amended) The method of Claim 28, wherein a gene expression microarray is used to detect the level of expression of *laminin* α4-specific mRNA.

35.(Reiterated) The method of Claim 28, further comprising detecting quantitatively or semi-quantitatively in the sample a level of expression with respect to a normal tissue control, of a gene encoding a protein selected from the group consisting of insulin-like growth factor binding protein precursor 3, transforming growth factor-β-induced gene, vascular endothelial growth factor, connective tissue growth factor, human insulin-like growth factor binding protein precursor 5, placental growth factor, transcription factor Ap-2, human insulin-like growth factor II, epidermal growth factor receptor, matrix metalloproteinase-2, keratin 18, vimentin, fibronectin 1, phospholipase A2 receptor, desmoplakin, tropomodulin, tenascin C, and collagen type IV α1 chain, or detecting a combination of expression levels for any of these.

A7

36.(Amended) The method of Claim 28, further comprising detecting the overexpression of *laminin* β1-specific mRNA relative to the normal tissue control.

A8

44.(Amended) A method of predicting the recurrence of a glioma in a human subject from whom a glioma has been resected, comprising:

A8 concld

(a) obtaining a tissue sample from the brain of the human subject, said tissue sample being from a region adjacent to the site of the glioma;

(b) detecting quantitatively or semi-quantitatively a level of expression for *laminin* α4-specific mRNA in the sample; and

(c) comparing the expression level in (b) to a level of expression in a normal tissue control, wherein overexpression of *laminin* α4-specific mRNA, with respect to the control, is predictive of a recurrence of glioma in the subject.

45.(Reiterated) The method of Claim 44, wherein the tissue sample is histopathologically normal in appearance.

A9

48.(Amended) The method of Claim 44, wherein the expression level of *laminin* α4-specific mRNA is detected by measuring RNA.

49.(Amended) The method of Claim 44, wherein the expression level of *laminin* α4-specific mRNA is detected by measuring cDNA.

50.(Amended) The method of Claim 44, wherein a gene expression microarray is used to detect the level of expression of *laminin* α4-specific mRNA.

51.(Reiterated) The method of Claim 44, further comprising detecting quantitatively or semi-quantitatively in the sample a level of expression with respect to a normal tissue control, of a gene encoding a protein selected from the group consisting of insulin-like growth factor binding protein precursor 3, transforming growth factor-β-induced gene, vascular endothelial growth factor, connective tissue growth factor, human insulin-like growth factor binding protein precursor 5, placental growth factor, transcription factor Ap-2, human insulin-like growth factor II, epidermal growth factor receptor, matrix metalloproteinase-2, keratin 18, vimentin, fibronectin 1, phospholipase

A2 receptor, desmoplakin, tropomodulin, tenascin C, and collagen type IV α1 chain, or detecting a combination of expression levels for any of these.

A10

52.(Amended) The method of Claim 44, further comprising detecting the overexpression of *laminin* β1-specific mRNA relative to the normal tissue control.

53.(Reiterated) A method of predicting recurrence of a glioma in a human subject from whom a glioma has been resected, comprising:

(a) obtaining a tissue sample from the brain of a human subject, said tissue sample being from a region adjacent to the site of the glioma, said sample comprising a cell expressing a plurality of mRNA species that are detectably distinct from one another;

(b) detecting quantitatively or semi-quantitatively an expression level for *laminin* α4-specific mRNA; and

(c) comparing the expression level in (b) to a level of expression in a normal tissue control, wherein overexpression of *laminin* α4-specific mRNA, with respect to the control, is predictive of a recurrence of glioma in the subject.

54.(Reiterated) The method of Claim 53, wherein a gene expression microarray is used to detect the level of expression of *laminin* α4-specific mRNA.

55.(Reiterated) The method of Claim 54, wherein the expression level of *laminin* α4-specific mRNA is detected by measuring RNA.

56.(Reiterated) The method of Claim 54, wherein the expression level of *laminin* α4-specific mRNA is detected by measuring cDNA.

57.(Reiterated) The method of Claim 53, further comprising detecting quantitatively or semi-quantitatively in the sample a level of expression with respect to a normal tissue control, of a growth

factor-related gene encoding a protein selected from the group consisting of insulin-like growth factor binding protein precursor 3, transforming growth factor-β-induced gene, vascular endothelial growth factor, connective tissue growth factor, human insulin-like growth factor binding protein precursor 5, placental growth factor, transcription factor Ap-2, human insulin-like growth factor II, and epidermal growth factor receptor, whereby the relative aggressiveness of the glioma is predicted.

58.(Reiterated) The method of Claim 53, further comprising detecting quantitatively or semi-quantitatively in the sample a level of expression with respect to a normal tissue control, of a structural gene encoding a protein selected from the group consisting of matrix metalloproteinase-2, keratin 18, vimentin, fibronectin 1, phospholipase A2 receptor, desmoplakin, tropomodulin, tenascin C, and collagen type IV α1 chain, whereby the relative invasiveness of the glioma is predicted.

59.(Reiterated) The method of Claim 53, further comprising detecting the overexpression of *laminin* β1-specific mRNA relative to the normal tissue control.

60.(Reiterated) A method of classifying the grade of a malignant tumor in a human subject, comprising:

(a) obtaining a tissue sample from the human subject, said sample comprising a cell expressing a plurality of mRNA species that are detectably distinct from one another;

(b) detecting quantitatively or semi-quantitatively an expression level for at least two of the plurality of mRNA species, wherein at least one of the detected mRNA species is a *laminin* α4-specific mRNA and at least one is specific to a growth factor-related gene or to a structural gene other than a *laminin* gene;

(c) constructing an expression profile of the sample comprising a combination of the detected expression levels of *laminin* α4-specific mRNA and the at least one other mRNA species specific to the growth factor-related gene or to the structural gene other than a *laminin* gene; and

(d) comparing the expression profile in (c) to an expression profile for a normal tissue control, wherein overexpression of *laminin* α4-specific mRNA, with respect to the control, is

indicative of the presence and relatively high invasiveness of the tumor in the subject, wherein overexpression of the structural gene other than a *laminin* gene is indicative of relatively high tumor invasiveness, and wherein overexpression of the growth factor-related gene is indicative of relatively high tumor aggressiveness.

61.(Reiterated) The method of Claim 60, wherein the growth factor-related gene encodes a protein selected from the group consisting of insulin-like growth factor binding protein precursor 3, transforming growth factor-β-induced gene, vascular endothelial growth factor, connective tissue growth factor, human insulin-like growth factor binding protein precursor 5, placental growth factor, transcription factor Ap-2, human insulin-like growth factor II, and epidermal growth factor receptor.

62.(Reiterated) The method of Claim 60, wherein the structural gene encodes a protein selected from the group consisting of matrix metalloproteinase-2, keratin 18, vimentin, fibronectin 1, phospholipase A2 receptor, desmoplakin, tropomodulin, tenascin C, and collagen type IV α1 chain.

63.(Reiterated) The method of Claim 60, wherein the expression level of *laminin* α4-specific mRNA is detected by measuring RNA.

64.(Reiterated) The method of Claim 60, wherein the expression level of *laminin* α4-specific mRNA is detected by measuring cDNA.

65.(Reiterated) The method of Claim 60, wherein a gene expression microarray is used to detect the level of expression of *laminin* α4-specific mRNA.

66.(Reiterated) The method of Claim 60, further comprising detecting the overexpression of *laminin* β1-specific mRNA relative to the normal tissue control.

67.(Reiterated) The method of Claim 60, wherein the tissue sample is brain tissue.

68.(Reiterated) The method of Claim 60, wherein the tumor is a glial tumor.

Please add the following new Claims 75-78.

All

--75.(New) The method of Claim 1, further comprising detecting the overexpression of a gene encoding laminin β1 subunit relative to the normal control.

76.(New)The method of Claim 18, further comprising detecting the overexpression of a gene encoding laminin β1 subunit relative to the normal control.

77.(New)The method of Claim 28, further comprising detecting the overexpression of a gene encoding laminin β1 subunit relative to the normal control.

78.(New)The method of Claim 44, further comprising detecting the overexpression of a gene encoding laminin β1 subunit relative to the normal control.--.

REMARKS

The Office Action and Applicant's Election of Designated Claim Group and Amendment

The Examiner required restriction, under 35 U.S.C. § 121, and required Applicant to elect a single invention to which the claims must be restricted.

The Examiner designated the following two claim groups:

1. Group I; Claims 1-11, 16-19, 24-30, 35-37, 42-46, 51-52, and 69-74, which the Examiner characterized as being drawn to methods for detecting a malignant tumor, diagnosing glioma, predicting a recurrence of a malignant tumor, using protein.

2. Group II; Claims 1-10, 12-18, 20-29, 31-36, 38-45, and 47-68, which the Examiner characterized as being drawn to methods for detecting a malignant tumor, diagnosing glioma, predicting a recurrence of a malignant tumor, using mRNA.

In response, Applicant elects **Group II**. Applicant's election is made with a complete reservation of all rights under 35 U.S.C. § 121.

In view of the restriction requirement and Applicant's election of designated claim Group II, Applicant has canceled Claims 11, 12, 19, 20, 30, 31, 37-42, 46, 47, and 69-74, without prejudice, as being directed to a non-elected claim group (e.g., Claims 11, 19, 30, 37, 46, and 69-74) or as being made redundant by other amendments herein (e.g., Claims 12, 20, 31, 38-43, and 47).

Further, Applicant has amended Claims 1, 16, 18, 36, and 52, to delete the recitation of the phrases (1) "or protein", (2) "laminin α4 subunit protein or", and (3) "laminin β1 subunit protein or", as being directed to non-elected subject matter.

Claims 13-15, 21, 22, 23, 32-34, and 48-50 have been amended to delete the dependencies from now canceled claims and to change those dependencies to be from still pending claims.

Claims 36 and 52 have been amended for greater clarity to recite "laminin β1-specific mRNA" instead of "laminin β1-specific nucleic acid."

New Claims 75-78 are supported in the specification as originally filed, for example, at page 50, line 1 through page 51, line 16, and at page 53, Table7.

Respectfully submitted,

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